Remarks

Claims 1-6, 8, 9, and 39-42 are pending in the subject application and currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Claims 1-6, 8, 9, and 39-42 are rejected under 35 USC §112, first paragraph, as nonenabled by the subject specification. Applicants note that the Examiner acknowledges that the specification enables methods of inhibiting intimal hyperplasia at a site in a blood vessel by periadventitial administration of a DNA expression vector encoding VEGF. However, the Examiner asserts that the specification does not enable treatment of vascular disorders in any species other than a rabbit. Applicants respectfully traverse this ground of rejection.

In a first aspect of the rejection, the Examiner asserts that the treatment of vascular disorders in general by delivery of VEGF-encoding nucleic acids was unpredictable and, thus, the present invention is not enabled for treatment of non-specific vascular disorders. Applicants respectfully submit that claims 1-6, 8, and 9 are not directed to treatment of vascular diseases in general. Rather, the claims specifically recite treatment or inhibition of intimal hyperplasia. Thus, Applicants respectfully assert that this aspect of the rejection has been obviated.

In another aspect of the rejection, set forth at pages 5-8 of the Office Action, the Examiner maintains that small animal models of intimal hyperplasia disease and treatment are not predictive of success in other animals, particularly humans. Applicants respectfully maintain that small animal models are reasonably correlated with the human disease condition and are predictive of success in other animals, including humans. Applicants assert that for studies directed to treatment of blood vessels in mammals, the rabbit animal model is, and has been, accepted in the art and has been used extensively in studies reported in the scientific literature. The Strauss *et al.* (*Int. J. Radiation Oncology Biol. Phys.*, 2002, Vol. 54, No. 2) and Farb *et al.* (*Circulation*, 2001, Vol. 103) references, which have been previously submitted, are examples of references that show that the rabbit is a suitable animal model and is still being used in studies for testing suitability of procedures in humans. If the rabbit model was not reasonably correlated with disease in humans, Applicants respectfully assert that clinical researchers would cease using it for their studies and it is unlikely that studies using rabbits would continue to be published in the scientific literature. While there may be some agents or methods unrelated to the subject invention that may have worked in rabbit models

that subsequently may not have successfully transferred when attempted in humans, this does not exclude the rabbit model as a valid and useful animal model. Animal models used for addressing issues of enablement do not have to provide perfect correlation with treatment in humans; there only has to be a reasonable correlation. Applicants maintain that the fact that the rabbit model has been used extensively in the past and continues to be used in current scientific studies is evidence that the rabbit was, and remains, a valid model for other mammals, including humans. In addition to the rabbit model, Applicants have also submitted data in the subject application which shows that the claimed method is efficacious on pig blood vessels. This animal model data, which has been deemed insufficient by the Patent Office, was sufficient for the U.S. Food and Drug Administration (FDA) to approve Applicants' invention for testing in human clinical trials, the results of which are discussed in more detail below.

Applicants submit herein for the Examiner's attention that the FDA accepted the results from the phase I human clinical trials of the subject invention (which were previously reported to the Examiner in the subject application), and has approved **phase II** human clinical trials. Applicants have attached with this Response press releases from Ark Therapeutics Ltd. (the assignee of record of the subject application) indicating that Ark Therapeutics' Investigational New Drug (IND) application has moved from phase I to phase II clinical trials.

The July 2005 Press Release from Ark Therapeutics submitted herewith reports that the first stage (a low dose study) of the phase II human clinical trials has been completed, with the results having been presented at the American College of Surgeons annual meeting in October. As indicated in the Release, six patients having kidney failure were treated with the subject invention following vascular graft access surgery for dialysis. Based on the results of the first stage, the Data Safety Monitoring Board granted clearance to proceed to higher dose studies. The October 18, 2005 Press Release from Ark Therapeutics discusses those results from the first stage of the phase II trials. The Press Release discloses that the access grafts of five of the six patients (one patient was withdrawn from the study due to an infection related to the surgical procedure and not the treatment) that received a dosage of $4x10^9$ particles remained functional three times longer than that obtained with previous graft access procedures. The mean patency of previously performed access procedures in these patients was 4.5 months; however, in the phase II trial, the graft patency was extended to at

least 14 months with all of the grafts remaining functional for dialysis. Thus, the phase II clinical trial shows that a significant number of treated patients had prolonged graft patency. Higher dosage studies in the phase II trial remain ongoing.

Although it is clear that the standards of therapeutic efficacy required by the Patent Office for a therapeutic treatment for purposes of enablement are not higher than standards of the FDA for evaluating a drug or treatment, the Patent Office maintains that the claimed method is not enabled for humans, even though human clinical trials have been approved by the FDA and, as reported herein, those trials have met with success sufficient for the FDA to allow higher dosage studies to proceed. Applicants have established therapeutic efficacy of the claimed method in acceptable animal models, *e.g.*, rabbits and pigs, and based on the results in these animal models, the FDA has approved clinical trials on humans. Applicants have also demonstrated that the **clinical trials in humans** have met with therapeutic efficacy and success. In contrast, based on the same animal models and data accepted by the FDA for grant of human trials, the Patent Office has maintained that the claimed method is not enabled for animals other than rabbits. In view of the above remarks and evidence, Applicants respectfully assert that the claimed methods meet the enablement requirements of the patent statute. Reconsideration and withdrawal of the rejection under 35 USC §112, first paragraph, is respectfully requested.

Claims 1-6, 8, 9, and 39-42 are provisionally rejected under the judicially created doctrine of "obviousness-type" double patenting over claims 16, 18, 20-25, 27, 33, and 34 of co-pending Application No. 10/196,345. Applicants acknowledge that a terminal disclaimer can be filed to overcome this rejection. Upon the Examiner's indication of allowable subject matter in the subject application, a terminal disclaimer or other appropriate action will be taken.

In view of the foregoing remarks, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

Doran R. Pace
Patent Attorney
Registration No. 38,261
Phone No.: 352-375-8100
Fax No.: 352-372-5800
Address: P.O. Box 142950
Gainesville, FL 32614-2950

DRP/kmm
Enclosures: July 2005 Press Release from Ark Therapeutics; October 18, 2005 Press Release from Ark Therapeutics.